

SPECIFICATION

PATCH ACTIVATED IN USE

5 Technical Field

The present invention relates to a patch activated in use, and more particularly, to a patch activated in use that is used after activation of a drug by supplying a dissolution liquid immediately before use.

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Background Art

When a patch containing a chemically labile drug is manufactured by a conventional method, the stability of the drug is generally ensured by studying the composition 15 (formulation) of the preparation. However, in some cases, sufficient stability of a drug may not be obtained by the study of formulation depending upon the nature of the drug.

Then, as a technique for stabilizing a drug, there is known that the drug is previously made in a solution form, 20 stored in a container, and supplied to a drug permeable layer by breaking the container when used. For example, Patent Document 1 discloses a dermatologic patch for external use having a flowable drug enclosed in a blister portion. The dermatologic patch is formed of an adhesive sheet and a release 25 sheet. The adhesive sheet has a blister portion formed of a blister and a drug coating layer, which seals the lower surface of the blister, and a drug permeating layer formed under the

drug coating layer. When used, the user presses the blister by a finger, thereby breaking the drug coating layer to transfer a fresh drug into the drug permeating layer. The dermatologic patch has a concave or convex protrusion provided to the blister 5 or enclosed within the blister portion. The protrusion functions not only to break the drug coating layer easily and without fail but also to give direct acupressure or stimulate an acupressure point.

Patent Document 1: Japanese Patent Application Laid-Open
10 No. 9-124468

On the other hand, another patch is known, which is used by supplying a liquid to a dry drug. For example, Patent Document 2 discloses an adhesive bandage having a piece of gauze at the center of an adhesive tape. The adhesive bandage 15 is formed by placing a piece of sterilized dry gauze containing a disinfectant or a therapeutic drug at the center of the adhesive surface of the adhesive tape, adhering an immobilizing end to the adhesive surface of the adhesive tape, providing an adhesive surface cover so as to cover the gauze, and providing 20 a liquid pouch covered by a easy-to-break thin film material, which is less stronger than the adhesive surface cover, to the portion facing the gauze of the adhesive surface cover. In the pouch, sterilizing liquid or sterilized distilled water 25 is contained. In using, when the user strongly presses the adhesive cover to break the thin film, the gauze gets wet with a disinfectant solution or sterilized distilled water

contained in the liquid pouch to effectively produce the medicinal effect of the drug.

Patent Document 2: Japanese Utility Model Publication No. 54-23197

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Disclosure of the Invention

Problems to be Solved by the Invention

These conventional techniques have problems. In the technique disclosed in Patent Document 1, a drug solution is supplied to a drug permeable layer by breaking a container when used. This technique is applicable to a drug that can be stored stably in a solution, but unfavorable to other drugs that are unstable in a solution, in view of stability. Also, in the technique disclosed in Patent Document 2, a liquid is supplied to a dry drug, when used. In this case, the liquid pouch is covered with an easy-to-break thin material, so that the portion of the pouch that is broken when the adhesive cover is pressed is not determined. For example, if the thin film of the pouch breaks at its end, the liquid may not be spread all over the gauze.

Thus, an object of the present invention is to provide a patch activated in use with which a drug can be activated uniformly by supplying a solution, when used.

25 Means for Solving the Problems

The aforementioned object can be attained by a patch activated in use comprising: an absorber containing a dry drug

and formed of a material capable of absorbing a liquid; a wall material arranged around the absorber and having an adhesive layer on the lower surface thereof; a support arranged on the absorber and the wall material and having an opening at the 5 center; a diaphragm arranged on the support; and a dissolution liquid reservoir arranged on the diaphragm, holding a dissolution liquid dissolving the drug in a space with the diaphragm, and having a protruding portion which breaks the diaphragm by pressure. The patch may further have a solution 10 permeable film on the lower surface of the absorber. Also, on the lower surface of the absorber and the adhesive layer, a liner having a concaved portion facing the absorber may be provided.

Another patch activated in use according to the present 15 invention comprising: a drug containing layer containing a dry drug; an absorber arranged on the drug containing layer and formed of a material capable of absorbing a liquid; a wall material arranged around the absorber and having an adhesive layer on the lower surface thereof; a support arranged on the absorber and the wall material and having an opening at the 20 center; a diaphragm arranged on the support; and a dissolution liquid reservoir arranged on the diaphragm, holding a dissolution liquid dissolving the drug in a space with the diaphragm, and having a protruding portion which breaks the 25 diaphragm by pressure. In the patch, a liner having a concaved portion facing the drug containing layer may be provided on

the lower surface of the drug containing layer and the adhesive layer.

Another patch activated in use according to the present invention comprising: a support; an absorber arranged on the support, containing a dry drug, and formed of a material capable of absorbing a liquid; a wall material arranged on the support and around the absorber and having an adhesive layer on the upper surface thereof; a liner arranged on the absorber and the adhesive layer and having an opening at the center,

10 a diaphragm arranged on the liner; and a dissolution liquid reservoir arranged on the diaphragm, holding a dissolution liquid dissolving the drug in a space with the diaphragm, and having a protruding portion which breaks the diaphragm by pressure. In the patch, a solution permeating film can be

15 provided on the upper surface of the absorber.

Another patch activated in use according to the present invention comprising: a support; an absorber arranged on the support and formed of a material capable of absorbing a liquid; a wall material arranged on the support and around the absorber and having an adhesive layer on the upper surface thereof;

20 a drug containing layer arranged on the absorber and containing a dry drug; a liner arranged on the drug containing layer and the adhesive layer and having an opening at the center; a diaphragm arranged on the liner; and a dissolution liquid reservoir arranged on the diaphragm, holding a dissolution liquid dissolving the drug in a space with the diaphragm, and

having a protruding portion which breaks the diaphragm by pressure.

In the patch, a portion of the diaphragm in contact with the dissolution liquid may have an oval shape and the protruding portion of the dissolution liquid reservoir may have a linear top end portion extending along the longitudinal axis of the oval. In this case, assuming that the length of the linear top end portion is represented by L1 and the length of the longitudinal axis of the portion of the diaphragm in contact with the dissolution liquid is represented by L2, the following relationship is preferably satisfied.

$$0.1 \times L2 \leq L1 \leq 0.5 \times L2$$

Furthermore, a portion of the diaphragm in contact with the dissolution liquid may have a circular shape and the protruding portion of the dissolution liquid reservoir may have a cruciform top end portion. In this case, assuming that the lengths of both bars of the cruciform top end portion are represented by L10 and L11, respectively, and the diameter of the portion of the diaphragm in contact with the dissolution liquid is represented by L2, the following relationship is preferably satisfied.

$$0.1 \times L2 \leq L10 \leq 0.5 \times L2 \text{ and/or } 0.1 \times L2 \leq L11 \leq 0.5 \times L2$$

Furthermore, the portion of the support around the opening is preferably depressed toward the absorber compared to the other portion. Moreover, the support inclines from the peripheral portion toward the opening while depressed toward the absorber. Similarly, the portion of the liner around the

opening is depressed toward the absorber compared to the other portion. Also, the liner inclines from the peripheral portion toward the opening with respect to the absorber.

The dissolution liquid reservoir is preferably formed by subjecting a sheet material to mold processing and the sheet material preferably has a water vapor permeability of 0.22 g/m²·24 hr or less. The sheet material preferably has a thickness of about 250 μm to about 350 μm . The sheet material may contain, for example, a cyclic polyolefin copolymer film, and preferably, a laminate film of a cyclic polyolefin copolymer film and a polyolefin film. The sheet material may include a fluorocarbon resin film, and preferably a laminate film of a fluorocarbon resin film and a polyolefin film. Furthermore, the diaphragm may be an aluminium foil.

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Advantages of the Invention

According to the present invention, it is possible to obtain a patch activated in use with which a drug can be activated uniformly by supplying a dissolution liquid, when used. When the dissolution liquid is supplied in the manner according to the present invention, the concentration of a drug can be virtually equalized at all parts of the patch. Furthermore, the solution of the dissolution liquid reservoir can quickly flow when used, so that the amount of solution remaining in the dissolution liquid reservoir can be reduced.

Brief Description of the Drawings

Figure 1 (a) is a plan view of a structure of a patch activated in use according to the present invention and Figure 1(b) is a sectional view taken along the line X-X of the Figure 1 (a);

5 Figure 2 is a sectional view of another structure of the patch activated in use according to the present invention;

Figure 3 is a sectional view of another structure of the patch activated in use according to the present invention;

10 Figure 4 is a sectional view of another structure of the patch activated in use according to the present invention;

Figure 5 is a sectional view of another structure of the patch activated in use according to the present invention;

Figure 6 is a sectional view of another structure of the patch activated in use according to the present invention;

15 Figure 7 is a sectional view of still another structure of the patch activated in use according to the present invention;

Figure 8 is a sectional view of still another structure of the patch activated in use according to the present invention;

20 Figure 9 (a) is a plan view of a structure of a dissolution liquid reservoir for use in a patch activated in use according to the present invention, Figure 9(b) is a sectional view taken along the line X-X of the Figure 9 (a), and Figure 9(c) is a sectional view taken along the line Y-Y of the Figure 9(a);

Figure 10 is a plan view of another structure of the dissolution liquid reservoir for use in a patch activated in use according to the present invention;

Figure 11 is a sectional view showing a structure of a support or a liner according to the present invention; and

Figure 12 is a sectional view showing another structure of a support or a liner according to the present invention.

Description of Symbols

10 10, 40 Drug

11, 41 Absorber containing a dry drug

12, 42 Adhesive layer

13, 43 Wall material

14, 44 Opening

15 15, 45 Support

16, 46, 91 Dissolution liquid

17, 47, 94 Protruding portion

18, 48, 90 Dissolution liquid reservoir

19, 49, 79, 89 Liner

20 20, 50, 92 Diaphragm

21, 51 Solution permeable film

31, 61 Absorber containing no drug

32, 62 Drug containing layer

25 Best Mode for Carrying Out the Invention

Figure 1 (a) is a plan view of a structure of a patch activated in use according to the present invention and Figure

1(b) is a sectional view taken along the line X-X of the Figure 1 (a). As shown in the figures, a patch activated in use of this embodiment comprises an absorber 11 containing a dry drug 10 and formed of a material capable of absorbing a liquid, 5 a wall material 13 arranged around the absorber 11 and having an adhesive layer 12 on the lower surface thereof, a support 15 arranged on the absorber 11 and the wall material 13 and having an opening 14 at the center, a diaphragm 20 arranged on the support 15, and a dissolution liquid reservoir 18 10 arranged on the diaphragm 20 holding a dissolution liquid dissolving the drug in a space with the diaphragm 20, and having a protruding portion 17 which breaks the diaphragm 20 by pressure. The protruding portion 17 has a linear top end portion as shown in the figure, for example, and arranged in 15 contact or in the proximity of the diaphragm 20. On the lower surface of the absorbent 11 and the adhesive layer 12, a liner 19 is detachably attached. In this embodiment, the dissolution liquid reservoir 18 and the diaphragm 20 may be separately or integrally formed. A dissolution liquid 20 container is formed of the dissolution liquid reservoir 18 and the diaphragm 20 in combination. The shape of the opening 14 of the support is not particularly limited. Any shape may be employed as long as it can supply the solution uniformly to the absorber 11, for example, a circular shape is preferable. 25 In this case, the dimension of the opening varies depending upon the size of the absorber 11, for example, the opening has a diameter of 2 to 10 mm, and preferably 4 to 8 mm. Note

that the support 15 may be omitted and instead, the diaphragm may substitute the function of the support. In this case, an opening is not previously provided. The opening comes to be provided by a protruding portion when used.

5 In using, when the user presses the upper surface of the dissolution liquid reservoir 18 or the protruding portion 17, the protruding portion 17 breaks the diaphragm 20. At this time, the diaphragm 20 greatly breaks along the liner top end portion, with the result that the solution in the dissolution 10 liquid reservoir 18 flows through the opening 14 of the support 15 to the absorber 11. By virtue of the solution, the absorber 11 gets wet to activate a drug 10 uniformly. Thereafter, the liner 19 is removed and the patch of the present invention 15 is applied to the skin. In this manner, an activated drug 20 is permeated into the skin. In this embodiment, the dissolution liquid reservoir 18 is fixed to the patch itself. Therefore, the patch may be applied without waiting until the dissolution liquid reservoir becomes empty. This is because even if the dissolution liquid remains in the dissolution 25 liquid reservoir 18 when used, it is gradually supplied to the absorber 11.

 In the patch according to the present invention, the following substances may be used in individual portions. As a drug, any type of drug may be used depending upon the 25 therapeutic purpose. As long as a compound has a pharmacological activity, it is not particularly limited by the type of drug, type of a salt, and application of drug.

Example of such a compound may include antibiotic, antifungal drug, antitumor drug, cardiac stimulant, antiarrhythmic, vasodilator, antihypertensive drug, diuretic drug, antihypertensive/diuretic drug, drug for circulatory organs, 5 antiplatelet drug, hemostatic drug, hypolipidemic drug, antipyretic/analgesic/antiinflammatory drug, antirheumatic drug, muscle relaxant, antitussive and expectorant, antiulcer drug, sedative drug, antiepileptic drug, antidepressant drug, antiallergic drug, diabetic diabetes mellitus therapeutic 10 drug, antituberculous drug, hormone drug, narcotic antagonist, bone absorption suppressing drug, neovascularization suppressing drug, and local narcotic drug.

Examples of the antibiotic include gentamicin sulphate, lividomycin, sisomicin sulfate, tetracycline hydrochloride, 15 ampicillin, cefalotin sodium, cefotiam hydrochloride, cefazolin sodium, thienamycin, sulfazecin, streptomycin sulfate, kanamycin sulfate, rifampicin, vancomycin hydrochloride, ofloxacin, and cefoselis sulfate.

Examples of the antifungal agent include amphotericin 20 B, itraconazole, fluconazole, miconazole, 2-[(1R,2R)-2-(2,4-difluoro phenyl-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propoxy)-4-[4-2,2,3,3-tetrafluoropropoxy]phenyl]-3(2H,4H)-1,2,4-triazolon.

25 Examples of the antitumor agent include bleomycin hydrochloride, tegafur, actinomycin D, mitomycin C, adriamycin, fluorouracil, 6-mercaptopurine, cytarabine,

procarbazine, doxorubicin hydrochloride, methotrexate, and tamoxifen citrate.

Examples of the antituberculous agent include streptomycin sulfate, kanamycin sulfate, isoniazid, 5 ethambutol hydrochloride, and pyrazinamide.

Examples of the cardiac stimulant include tranc-e-bio Kiso camphor, teofirof, dopamine hydrochloride, dobutamine hydrochloride, and ubidecarenone.

Examples of the antiarrhythmic include propranolol 10 hydrochloride, oxyprenolol, procainamide hydrochloride, lidocaine, phenytoin, metoprolol tartrate, verapamil hydrochloride, and diltiazem hydrochloride.

Examples of the vasodilator include oxyfedrine hydrochloride, tolazoline hydrochloride, bamethan sulfate, 15 nicardipine hydrochloride, verapamil hydrochloride, and papaverine hydrochloride.

Examples of the antihypertensive drug include hydralazine hydrochloride, budralazine, prazosin hydrochloride, doxazosin mesilate, carteolol hydrochloride, 20 clonidine hydrochloride, enalapril maleate, captopril, delapril hydrochloride, manidipine hydrochloride, pinacidil, minoxidil, losartan, candesartan cilexetil, valsartan, telmisartan, and irbesartan.

Examples of the diuretic drug include acetazolamide, 25 methazolamide, chlorothiazide, furosemide, triamterene, amiloride, and aminometrozin.

Examples of the antihypertensive/diuretic drug include include pentolinium, and hexamethonium bromide.

Examples of the drug for circulatory organs include alprostadil, alprostadil alfadex, limaprost, ozagrel sodium, 5 clopidogrel sulfate, prostacyclin, beraprost, ciprostene, ailoprost, ataprost, clinprost, ethyl icosapentate, etilefrine hydrochloride, dihydroergotamine mesylate, pamicogrel, tranilast, probucol, candesartan cilexetil, sodium citrate, heparin, low molecular weight heparin, 10 nifedipine, efondipine hydrochloride, diltiazem hydrochloride, and tranilast.

Example of the antiplatelet drug include ticlopidine, satigrel, limaprost alfadex, clinprost, clopidogrel sulfate, sibrafiban, epitibatide, tirofiban hydrochloride, 15 sarpogrelate hydrochloride, xemilofiban hydrochloride, orbofiban acetate, isbogrel, cilostazol, aspirin, and abciximab.

Examples of the hemostatic drug include epinephrine, menadione sodium bisulfite, acetomenaphthone, and tranexamic 20 acid.

Examples of the hypolipidemic drug include sodium pravastatin, simvastatin, fuvastatin sodium, crivastatin, and atorvastatin.

Examples of the antipyresis/analgesiac/ 25 antiinflammatory drug include aspirin, sodium salicylate, sulpyrine, indomethacin, diclofenac sodium, loxoprofen sodium, felbinac, zaltoprofen, piroxicam, nimesulide,

Meloxicam, celecoxib, tiaramide, emorfazole, buprenorphine, eptazocine hydrobromide, pentazocine, butorphanol tartrate, tramadol hydrochloride, Ketorolac, meperidine hydrochloride, morphine hydrochloride, morphine sulfate, hydro-morphine, 5 fentanyl citrate, fentanyl, and mofezolac.

Examples of the antirheumatic drug include methotrexate hydrochloride, sodiumaurothiomalate, auranofin, bucillamine, D-penicillamine, actarit, lobenzarit, mizoribine, salazosulfapyridine, and tacrolimus hydrate.

10 Examples of the muscle relaxant include pridinol methane sulfonate, tubocurarine chloride, eperisone hydrochloride, tizanidine hydrochloride, chlorphenesin carbamate, tolperisone hydrochloride, dantrolene sodium, baclofen, and lanperisone hydrochloride.

15 Examples of the antitussive and expectorant include ephedrine hydrochloride, codeine phosphate, picoperidamine hydrochloride, ambroxol, bromhexine hydrochloride, salbutamol sulfate, tulobuterol hydrochloride, formoterol fumarate, azelastine hydrochloride, ketotifen fumarate, and 20 picoperidamine.

Examples of the antiulcer drug include ornoprostil, cimetidine, famotidine, ranitidine hydrochloride, metoclopramide, omeprazole, and lansoprazole.

Examples of the sedative drug include chlorpromazine 25 hydrochloride, atropine sulfate, and fluphenazine enanthate.

Examples of the antiepileptic drug include phenytoin sodium, and ethosuximide.

Examples of the antidepressant drug include amitriptyline hydrochloride, imipramine hydrochloride, clomipramine hydrochloride, desipramine hydrochloride, maprotiline hydrochloride, and phenelzine sulfate.

5 Examples of the antiallergic agent include diphenhydramine, hydrochloride, tripelennamine hydrochloride, clemizole, d-chlorpheniramine maleate, cyproheptadine hydrochloride, ketotifen fumarate, epinastine, and tacrolimus hydrate.

10 Examples of the diabetes mellitus therapeutic drug include glymidine zodium, glipizide, metformin, tolbutamide, chlorpropamide, glibenclamide, acetohexamide, midaglizole, glimepiride, senaglinide, repaglinide, and pioglitazone hydrochloride.

15 Examples of the antituberculous drug include streptomycin sulfate, kanamycin sulfate, isoniazid, ethambutol hydrochloride, and pyrazinamide.

Examples of the hormone drug include β -estradiol, testosterone enanthate, prednisolone succinate, 20 dexamethasone sodium phosphate, and methimazole.

Examples of the narcotic antagonist include levallorphan tartrate, nalorphine hydrochloride, protamine, and naloxone.

Examples of the bone absorption suppressing drug include sulfur-containing alkyl aminomethylene bisphosphonate, 25 raloxifene, aendronate sodium, Incadronate Disodium, tibolone, simadronate, risedronate, clodronate disodium,

falecalcitriol, calcitriol, alpha calcitriol, didronel sodium, ipriflavone, and minodronic acid.

Examples of the neovascularization suppressing drug include arterialization depression steroid [see Science Vol. 5 221, page 719 (1983)] and fumagillol derivatives [such as monochloroacetylcarbamoylfumagillol, O-dichloroacetylcarbamoylfumagillol (see European Patent application Nos. 357,061, 359036, 386667 and 415294)].

Examples of the local anesthetic drug include lidocaine hydrochloride, tetracaine hydrochloride, procaine hydrochloride, benzocaine hydrochloride, etidocaine hydrochloride, prilocaine hydrochloride, dibucaine hydrochloride, bupivacaine hydrochloride, cocaine hydrochloride, ethylaminobenzoate, orthocaine hydrochloride, 15 oxethazaine hydrochloride, and mepivacaine hydrochloride.

In addition to drugs, a drug dissolution rate regulator, an additive(s) for stabilization, an adsorption inhibitor may be added.

As the absorber, a material capable of absorbing a liquid satisfactorily is selected. Examples of such a material include polyester (a polyethylene terephthalate), polysaccharides and cellulose derivatives (rayon, cotton), polyamide (nylon), porous materials such as a nonwoven fabric, cloth, gauze and sponge, and hydrophilic polymers (agar, 25 agarose, alginic acid, xanthan gum, guar gum, dextran, dextrin, Pullulan, chitosan, gelatine, carboxyvinyl polymer, polyacrylate, carboxymethyl cellulose salt, polyoxyalkylene,

polyvinyl alcohol, polyvinylpyrrolidone, and polyacrylamide), and ion exchange resin (amberlite, diaion, cholestyramine); however, nonwoven fabric such as fabric principally made of rayon is preferably used, for example.

5 As the wall material, a water-impermeable material is selected such as foaming polyolefin (PE, PP), foaming polyurethane, foaming polystyrene, foaming gum (e.g. polybutylene), foaming EVA, and foaming PVC; however, foaming polyolefin is preferably used.

10 As the adhesive layer, mention may be made of natural rubber, styrene-isoprene-styrene block copolymer, styrene-butadien gum, styrene-isoprene gum, polyisobutylene, polyisoprene, polyacrylate, and silicon gum; however, polyacrylate is preferably used, for example.

15 As the supporting material, a water-impermeable material is selected such as polyolefin, polyurethane, polystyrene, gum, EVA, PVC, and PET.

20 The dissolution liquid reservoir may be formed of a molded sheet obtained by molding a sheet material such as PET, PVC, PVDC, PP, PE, polystyrene, cyclic polyolefin (COC), Al and a laminate body of these in the dome form and forming a convex protruding portion within the dome, or a sheet having a high barrier property (such as PCTFE/PP series, PCTFE/PVC series, cyclic polyolefin/PP series), and Al deposition sheet and SiO₂ deposition sheet. When the user presses the convex protruding portion of the dissolution liquid reservoir, the diaphragm or at least one of the stacked structure of the diaphragm and

the support is broken. When the convex protruding portion has a conical form, the shape of the broken portion is a point. In this case, the permeation of the solution to the absorber is poor. Therefore, the breaking portion (top end portion 5 of the protruding portion) of the convex form is preferably liner or planar. The material of the dissolution liquid reservoir may be PCTFE(-CF₂-CFC₁-)_npoly(chloro-trifluoroethylene), or a COC cyclic polyolefin copolymer. The thickness of the sheet is, for example, 100 10 to 500 μm . As the material for the dissolution liquid reservoir, for example, PP, PP/COC/PP, and PCTFE/PP series may be used.

As the diaphragm (the film to be broken by the protruding portion), Al, PP, PE and a laminate body of them may be mentioned. When Al foil is used, it may be preferably coated in order 15 to prevent corrosion, as needed. The thickness of the diaphragm is, for example, 5 to 100 μm in the case of Al, 15 to 50 μm in the case of PP and PE.

Example of the solution include water, alcohols, polyhydric alcohols, surfactants, saccharides, pH modifiers 20 (organic and inorganic acids/base), salines, water soluble polymers, solubilizing agents, absorption accelerator, fats and oils, and preservatives. Preferable examples include purified water, glycerin, methylparaben (propylparaben, propylene glycol). Example of the liner include PET, PEN, 25 PP, PE, paper, Al, and a laminate of these. Preferably, PET is used. In addition, it is preferable to apply mold-releasing treatment such as silicon treatment to the surface of the liner.

Furthermore, the liner may be processed in a concave form so as not to come in contact with a member containing a drug.

Figure 2 is a sectional view showing another structure of a patch activated in use according to the present invention.

5 Difference of the patch of this embodiment from that of Figure 1 resides in that a solution permeable film 21 is provided on the lower surface of the absorber 11 containing a drug. The other portions are the same as those of Figure 1. The solution permeable film 21 is effective in holding the absorber 10 and further provided as holding means when a powdery substance is contained.

As the solution permeable film, a porous film or ion exchange membrane may be used. Examples of the porous film include PE, PP, cellulose, cellulose acetate, PET, and nylon. 15 Examples of the ion exchange membrane include a positive ion exchange membrane, a negative ion exchange membrane, and a composite charged membrane. Preferably a positive ion exchange membrane of a nylon series may be used. However, when nonwoven cloth is used as the absorber, the solution 20 permeable film may not be used.

Figure 3 is a sectional view of another structure of the patch activated in use according to the present invention. The patch of this embodiment is characterized in that the absorber 11 containing a drug of Figure 1 is divided into two 25 layers, an absorber 31 containing no drug and a drug containing layer 32 containing a drug. The other structural elements are the same as in Figure 1. The reason why the absorber 31

containing no drug and the drug containing layer 32 are separately formed is that the drug is brought into contact with a living body at a high concentration to maximize the absorption of a drug.

5 As the drug containing layer, a porous film or ion exchange membrane containing a drug may be used. Examples of the porous film may include PE, PP, cellulose, cellulose acetate, PET, and nylon. Examples of the ion exchange membrane include a positive ion exchange membrane, negative ion exchange membrane, 10 and an composite charged membrane. Preferably a positive ion exchange membrane of a nylon series may be used.

Figure 4 is a sectional view of another structure of the patch activated in use according to the present invention. Unlike from those of Figures 1 to 3, when the patch of this 15 embodiment is used, a dissolution liquid reservoir is removed. As shown in the figure, the patch of the embodiment comprises: a support 45, an absorbing material 41 arranged on the support 45, containing a dry drug 40, and formed of a liquid absorbable material, a wall material 43 arranged around the absorber 41 20 and on the support 45 and having an adhesive layer 42 on the upper surface, a liner 49 arranged on the absorber 41 and the adhesive layer 42 and having an opening 44 at the center, a diaphragm 50 arranged on the liner 49, and a dissolution liquid reservoir 48 arranged on the diaphragm 50, holding a solution 25 for dissolving a drug in a space with the diaphragm 50, and having a protruding portion 47 for breaking the diaphragm 50 by pressure.

The protruding portion 47 is constructed in the same manner as in Figure 1. The liner 49 is detachably attached to the adhesive layer 42. The shape and size of the opening 44 of the liner are the same as in Figure 1.

5 In using, when the user presses the upper surface of the dissolution liquid reservoir 48, the protruding portion 47 breaks the diaphragm 50. When the diaphragm 50 is broken by the pressure of the protruding portion 47, the solution inside the dissolution liquid reservoir flows out through the opening 10 44 of the liner 49 to the absorber 41. The absorber 41 gets wet by the solution to activate a drug uniformly. Thereafter, the liner 49 is removed together with the dissolution liquid reservoir 48 and then the patch is applied to the skin. In this 15 way, the activated drug permeates into the skin. In this embodiment, since the dissolution liquid reservoir 48 is removed together with the liner 49 from the main body of the patch when used, the patch is preferably applied after the solution completely flows out from the dissolution liquid reservoir 48.

20 Figure 5 is a sectional view of another structure of the patch activated in use according to the present invention. The difference of the patch of this embodiment from that of Figure 4 resides in that a solution permeable film 51 is provided on the upper surface of the absorber 41 containing a drug. 25 The other structural elements are the same as in Figure 4. The reason why the solution permeable film 51 is provided and

the material of the film are the same as described in connection with Figure 2.

Figure 6 is a sectional view of another structure of the patch activated in use according to the present invention.

5 The patch of this embodiment is characterized in that the absorber 41 containing a drug in Figure 4 is divided into two portions, an absorber 61 containing no drug and a drug containing layer 62 containing a drug. The other structural elements are the same as in Figure 4. The reason why the

10 absorber 61 and the drug containing layer 62 are separately formed and the material of the film are the same as described in connection with Figure 3.

Figure 7 is a sectional view of another structure of the patch activated in use according to the present invention.

15 The difference of the patch of this embodiment from that of Figure 1 resides in that a liner 79 having a concaved form facing the absorber is provided on the lower surface of the absorber and the adhesive layer. The other structural elements are the same as in Figure 1. The reason why the liner

20 79 is processed in the concaved form is to prevent the liner from being in contact with the member containing a drug.

Figure 8 is a sectional view of another structure of the patch activated in use according to the present invention.

The difference of the patch of this embodiment from that of

25 Figure 3 resides in that a liner 89 having a concaved form facing the drug containing layer is provided on the lower surface of the drug containing layer and the adhesive layer.

The other structural elements are the same as in Figure 3.

The reason why the liner 89 is processed in the concaved form is to prevent the liner from being in contact with the member containing a drug.

5 Figure 9 (a) is a plan view showing a structure of a dissolution liquid reservoir to be used in the patch activated in use according to the present invention, Figure 9(b) is a sectional view taken along the line X-X of the Figure 9(a), and Figure 9(c) is a sectional view taken along the line Y-Y 10 of the Figure 9(a). In this embodiment, the structure is designed such that the solution of the dissolution liquid reservoir can be supplied to the absorber to reduce the remaining amount of solution as much as possible. A dissolution liquid reservoir 90 of this embodiment stores a 15 solution 91 and has a protruding portion 93 for breaking a diaphragm 92 by pressure. As shown in the figure, the portion of the diaphragm 92 in contact with the solution has an oval shape and diaphragm 92 itself has a circular shape. The protruding portion 93 has a linear top end portion 94 extending 20 along the longitudinal axis of an oval-shape portion of the diaphragm 92 in contact with the solution. Assuming that the length of the top end portion 94 is represented by L1, and the length of the longitudinal axis of the portion of the diaphragm 92 in contact with the solution is represented by 25 L2, they are constructed so as to satisfy the following relationship:

$$0.1 \times L2 \leq L1 \leq 0.5 \times L2.$$

If so, when the protruding portion 93 is pressed in use and the diaphragm 92 is greatly broken along the linear top end portion, the solution 91 flows out well, with the result that the remaining amount of solution can be reduced. In this 5 embodiment, the top linear portion 94 is arranged at a distance from the diaphragm 92; however, they may be arranged in contact with each other.

Figure 10 is a plan view showing another structure of the dissolution liquid reservoir to be used in a patch activated 10 in use according to the present invention. The specific difference of the dissolution liquid reservoir 100 of the embodiment from that of Figure 9 resides in that the portion of the diaphragm 102 in contact with the solution is circularly formed in the same manner as in the diaphragm 102 and the 15 protruding portion 103 has a cruciform top end portion 104. Assuming that the lengths of the two bars of the cruciform top end portion 104 are represented by L10 and L11, respectively, and the diameter of the solution contact portion of the diaphragm 102 is represented by L2, they are constructed so 20 as to satisfy the following relationship:

$$0.1 \times L2 \leq L10 \leq 0.5 \times L2 \text{ and/or } 0.1 \times L2 \leq L11 \leq 0.5 \times L2.$$

In this way, when the protruding portion 103 is pressed in use and the diaphragm 102 is broken widely by the cruciform top end portion 104, the solution can flow out well, with the 25 result that the remaining amount of solution can be reduced.

Figure 11 is a sectional view showing a structure of the support or the liner according to the present invention. In

the embodiment, the structure is designed such that the solution is quickly supplied from the dissolution liquid reservoir to an absorber when used. The structure of the embodiment can be applied to the supporting bodies of Figures 5 1 to 3 and Figure 7 and 8, and to the liners of Figures 4 to 6. In the support 115 or the liner 119 of this embodiment, the portion around the opening 114 through which a solution flows is depressed toward the absorber compared to the other portion, that is, in the opposite side of the dissolution liquid 10 reservoir 118. By virtue of the structure, a space 110 is formed between the support 115 or the liner 119 and the dissolution liquid reservoir 118. When the dissolution liquid reservoir 118 is pressed in use, the diaphragm 113 is broken and a broken piece of the diaphragm can be spread in 15 the space 110, the solution can quickly flows through the opening 114, with the result that the remaining amount of solution can be reduced.

Figure 12 is a sectional view showing another structure of the support or the liner according to the present invention. 20 Also, in this embodiment, the structure is designed such that the solution stored in the dissolution liquid reservoir is quickly supplied to the absorber in use. The structure of the embodiment can be applied to the supporting bodies of Figures 1 to 3 and Figure 7 and 8, and to the liners of Figures 25 4 to 6. A support 125 or a liner 129 of the embodiment inclines from the peripheral portion toward an opening 124 with respect to the absorber, as shown in the figure. Also, in this case,

a space 120 is formed between the support 125 or the liner 129 and a dissolution liquid reservoir 128. When the dissolution liquid reservoir 128 is pressed in use and the diaphragm 123 is broken, the solution quickly flows through 5 the opening 124 without spreading to the peripheral portion, with the result that the remaining amount of solution in the dissolution liquid reservoir can be reduced.

The dissolution liquid container is formed of the dissolution liquid reservoir in combination with the diaphragm. 10 Now, a preferred structure of the dissolution liquid container will be described below. The dissolution liquid container has a dissolution liquid reservoir having a protruding portion processed to at least a portion. The protruding portion can be formed by molding so as to have a strength capable of breaking 15 the diaphragm by pressure. Therefore, a sheet (film) containing aluminium may not be used for forming the protruding portion since it is easily cracked or broken.

In the present invention, the sheet material (film) for use in the dissolution liquid container (dissolution liquid 20 reservoir) preferably has a water-vapor permeability of 0.30 g/m²·24 hr or less, and more preferably, 0.22 g/m²·24 hr or less. As such a sheet material, for example, a film containing a cyclic polyolefin copolymer (COC) and a fluorocarbon resin may be mentioned. Preferably, a fluorocarbon resin laminate 25 film may be used. Furthermore, if the inner surface of the container and the diaphragm can be sealed with heat, excellent airtightness can be obtained. For this reason, the

fluorocarbon resin laminate film is preferably laminated with polyvinyl chloride (PVC), polypropylene (PP) or polyethylene(PE) films. Furthermore, from a drug absorption point of view, a laminate film formed of these films and a 5 polypropylene or polyethylene film is more preferable. The thickness of the sheet material (film) is about 500 μm or less, preferably about 100 to 400 μm , more preferably about 250 to 350 μm , in view of breakability and processability. The diaphragm is preferably formed of aluminium foil.

10 Experimental Examples

Preparation of the dissolution liquid container

A dissolution liquid reservoir having a protruding portion shown, for example, in Figure 3, was formed by mold-processing. To the dissolution liquid reservoir, a 15 solution (600 μl of a 30 w/w% aqueous glycerin solution) was added and a processed aluminum foil (20 μm) on which an acrylic adhesive-material (DURO-TAK87-2516, 50 μm) is laminated at 140 to 150°C for 2 seconds is sealed with heat. In this manner, a dissolution liquid container was formed.

20 Preparation of a patch having a dissolution liquid integrated therein:

The acrylic adhesive material surface of the dissolution liquid container prepared above was adhered to the upper surface of a preparation to form the preparation shown, for 25 example, in Figure 3.

Preparation of patch having an alprostadil-containing solution integrated therein

The acrylic adhesive material surface of the dissolution liquid container prepared above was adhered to the upper surface of a preparation and a drug (alprostadil alfadex 5 mg) and lactose (8 mg) were added to a drug containing layer 5 of the preparation as shown, for example, in Figure 3, to prepare a preparation. The preparation thus prepared was stored in an aluminium package together with a desiccant (Tri sorb 1 g, manufactured by Sud-Chemie).

Now, Examples and Comparative Examples will be shown 10 below.

(Example 1)

The material of a dissolution liquid container (dissolution liquid reservoir) was a laminate of PE film/COC film/PE film (PE/COC/PE). The thickness of the laminate was 15 350 μm and a water-vapor permeability was 0.22 $\text{g}/\text{m}^2\cdot24\text{hr}$.

(Example 2)

The material of a dissolution liquid container (dissolution liquid reservoir) was a laminate of PP film/PCTFE film (fluorocarbon resin) film (PP/ PCTFE). The thickness 20 of the laminate was 300 μm and a water-vapor permeability was 0.11 $\text{g}/\text{m}^2\cdot24\text{hr}$.

(Example 3)

The material of a dissolution liquid container (dissolution liquid reservoir) was a laminate of PP film/PCTFE film (fluorocarbon resin) film (PP/ PCTFE). The thickness 25 of the laminate was 250 μm and a water-vapor permeability was 0.14 $\text{g}/\text{m}^2\cdot24\text{hr}$.

(Comparative Example 1)

The material of a dissolution liquid container (dissolution liquid reservoir) was a PVC film. The thickness of the film was 300 μm and a water-vapor permeability was 2.70
5 g/m²·24hr.

(Comparative Example 2)

The material of a dissolution liquid container (dissolution liquid reservoir) was a PP film. The thickness of the film was 300 μm and a water-vapor permeability was 0.70
10 g/m²·24hr.

(Comparative Example 3)

The material of a dissolution liquid container (dissolution liquid reservoir) was a PP film. The thickness of the film was 500 μm and a water-vapor permeability was 0.32
15 g/m²·24hr.

(Comparative Example 4)

The material of a dissolution liquid container (dissolution liquid reservoir) was a laminate of PE film/COC film/PE film (PE/COC/PE). The thickness of the laminate was
20 500 μm and a water-vapor permeability was 0.14 g/m²·24hr.

(Comparative Example 5)

The material of a dissolution liquid container (dissolution liquid reservoir) was a laminate of Al film/PP film (Al/PP). The thickness of the laminate was 150 μm and
25 a water-vapor permeability was 0 g/m²·24hr.

The Examples and Comparative Examples were evaluated for the processability of the protruding portion of the dissolution

liquid container and the breakability of the protruding portion through the diaphragm. The results shown in Table 1 were obtained.

5

Table 1 The material of container and properties

	Material of container	Thickness (μm)	Water-vapor permeability (g/m ²)	Processability of protruding portion	Breakability of diaphragm
Comparative Example 1	PVC	300	2.70	○	○
Comparative Example 2	PP	300	0.70	○	○
Comparative Example 3	PP	500	0.32	○	✗
Comparative Example 4	PE/COC/PE	500	0.14	○	✗
Comparative Example 5	Al/PP	150	0	✗	-
Example 1	PE/COC/PE	350	0.22	○	○
Example 2	PP/PCTFE	300	0.11	○	○
Example 3	PP/PCTFE	250	0.14	○	○

Water-vapor permeability: 40°C, 90%RH, 24hr (24 hours)

As shown in Table 1, in Examples 1 to 3, Comparative Examples 1 and 2, the protruding portion exhibited good processability and the diaphragm had good breakability 10 (symbol: ○). In Comparative Examples 3 and 4 (film thickness of about 500 μm), the protruding portion exhibited good processability (symbol: ○); however, the diaphragm had extremely poor breakability (symbol: ✗) since the strength 15 of the dissolution liquid container is high. In Comparative Example 5, breakage of aluminium was observed in the protruding portion during processing, and thus the processability of the protruding portion was poor (symbol: ✗).

Next, the weight change of the dissolution liquid container and deliver rate of the solution were evaluated depending upon temperature conditions. A patch integrated with a solution was prepared and stored for a month at 5 temperatures of 40 and 50°C, separately. The reduced amount of the solution (by percentage based on the initial amount) and the deliver rate of the solution were evaluated. The results shown in Table 2 were obtained. The deliver rate of the solution was evaluated based on the time required for 10 delivering of the solution over the entire surface of the drug holding film after the dissolution liquid container was pressed. That is, if the time is within about 30 seconds, symbol O was given and if the time is about 30 seconds or more, symbol x was given.

15

Table 2 Weight change and deliver rate of the solution depending upon temperature conditions

	Material of container	40°C, one month		50°C, one month	
		Reduction rate of solution	Deliver rate of solution	Reduction rate of solution	Deliver rate of solution
Comparative Example 1	PVC	15.3%	O	27.6%	x
Comparative Example 2	PP	5.9%	O	14.1%	O
Example 1	PE/COC/PE	2.0%	O	5.6%	O
Example 2	PP/PCTFE	0.3%	O	1.0%	O

The reduction rate of the solution suitable for long term 20 storage is desirably 13 % or less. The solutions of Examples 1 and 2 are suitable for long-term storage, since they exhibited

reduction rates of not more than 13% at temperatures of 40°C and 50°C. On the other hand, significant reduction rates of the solution were observed at temperatures of 40°C and 50°C in Comparative Example 1 and at a temperature of 50°C in 5 Comparative Example 2. They are not suitable for long-term storage. Furthermore, the time required for delivering the solution to a drug holding film for activating a drug in use was short in Example 1 and 2 and Comparative Example 2; however, long in Comparative Example 1.

10 When the results of Tables 1 and 2 are generalized, as shown in Examples 1 to 3, the sheet material (film) used in a dissolution liquid container (reservoir) preferably has a water vapor permeability of 0.22 g/m²·24hr or less and a thickness of about 250 µm to about 350 µm. Such a sheet contains 15 a cyclic polyolefin copolymer (COC) film and a fluorocarbon resin film, and is preferably a laminate of a cyclic polyolefin copolymer (COC) film and fluorocarbon resin film or a laminate of a fluorocarbon resin film and polyolefin film.

20 Industrial Applicability

The present invention is applicable to a patch for external use in the medical field. The present invention made it possible to provide a patch activated in use, having a dissolution liquid reservoir, being capable of maintaining 25 the stability of a drug, excellent in general use and practical use, and easily applicable. Furthermore, in the patch according to the present invention, since less amount of the

solution remains in the dissolution liquid reservoir when used, the drug contained in the patch can be ensured at a predetermined content.